

### **REMARKS/ARGUMENTS**

Claims 1-7, 10-20 and 23-81 were pending in the present application before the amendment as set forth above. Of them, claims 1-7, 10-20, 23, 24 and 75-81 were examined, and claims 25-74 were withdrawn as directed to non-elected subject matter. By the amendment, claims 1 and 12 are amended, and withdrawn claim 25-74 are canceled without prejudice. Applicants reserve every right in cancelled claims 8, 9, 21, 22 and 25-74 to file continuation applications. Applicant asserts that no new matter has been added.

In the March 28, 2008 Office Action, the Examiner rejected claims 1-4, 6, 10-15, 17, 19, 23, 24, 75, 76 and 78-80 under 35 U.S.C. §103(a) as being unpatentable over U.S. Pat. Pub. 2003/0107386 to Dodgson et al. (hereinafter “Dodgson”), in view of U.S. Patent No. 6,699,697 to Klemic et al. (hereinafter “Klemic”). Furthermore, claims 5, 7, 16, 18 and 20 were rejected under 35 U.S.C. §103(a) as being unpatentable over Dodgson and Klemic as applied to claims 2 and 12, and further in view of U.S. Patent No. 6,428,619 to Rubinsky et al. (hereinafter “Rubinsky”). Additionally, claims 77 and 81 were rejected under 35 U.S.C. §103(a) as being unpatentable over Dodgson and Klemic as applied to claims 1 and 12, and further in view of U.S. Patent Pub. 2002/0182627 to Wang et al. (hereinafter “Wang”).

Applicant appreciates the Examiner’s careful review of the application, and particularly thanks Examiner Bowers and Primary Examiner Beisner for granting and conducting a telephone interview with Mr. Christopher W. Glass, a Patent Attorney, and Dr. Peng Zhou, a Patent Agent for applicant on the record, April 17, 2008. Applicant also appreciates very much the professionalism shown by Examiner Bowers and Primary Examiner Beisner during the telephone interview.

During the telephone interview, the March 28, 2008 Office Action was discussed, and among other things, Examiner Bowers and Primary Examiner Beisner indicated that the use of a single substrate as a second substrate claimed in the present invention differentiated it from the cited references.

Any amendments to the claims not specifically referred to herein as being included for the purpose of distinguishing the claims from cited references are included for the purpose of clarification, consistence and/or grammatical/spelling correction only.

It is now believed that the application is in condition for allowance and such allowance is respectfully requested.

The following remarks herein are considered to be responsive thereto.

**Claims 1-7, 10, 11 and 75-77:**

As set forth above, amended claim 1 recites a device for monitoring status of at least one cell, wherein the cell has a membrane forming a substantially enclosed structure and defining an intracellular space therein, that requires:

- “a. a first substrate having a first surface and an opposite second surface;
- b. ***a second substrate*** supported by the first substrate, the second substrate having a first surface, an opposite second surface, a body portion between the first surface and the second surface, a first side surface and an opposite second side surface, wherein ***the body portion defines a first passage therein between the first side surface and the second side surface***, and a first opening on the first surface of the second substrate that is in fluid communication with the first passage;
- c. ***sidewalls positioned above*** the first surface of ***the second substrate***;
- d. ***a third substrate positioned over the sidewalls and the second substrate*** and having a first surface and an opposite second surface, wherein the third substrate, the sidewalls and the second substrate define a chamber, and wherein the chamber is in fluid communication with ***a second passage defined by portions of the sidewalls and the third substrate***;
- e. at least one sensor positioned in the first passage proximate to the first opening, wherein the cell is positioned in the chamber and the intracellular space of the cell is in fluid communication with the first passage through the first opening of the second substrate;
- f. at least one seal element positioned on the second substrate and proximate to the first opening, for sealing the cell to the second substrate in operation;
- g. ***a pair of first controls*** positioned inside the first passage, between the first surface of the first substrate and the second surface of the second substrate, for controlling the flow of a medium through the first passage; and

- h. *a second control* positioned inside the second passage, for controlling the flow of a medium through the second passage.” (Emphasis added.)

In the present application as originally filed, and particularly, in paragraphs from page 62, lines 25-32 to page 66, lines 1-22 of the specification and Figs. 5A, 5B and 5C of the drawings, several exemplary embodiments are disclosed of a device for monitoring status of at least one cell, wherein each cell has a membrane forming a substantially enclosed structure and defining an intracellular space therein.

In one embodiment, as shown in Figs. 5A, 5B, and 5C, which Fig. 5A is provided below, the device 500 has a first substrate 550 (530) with a first surface 551 and an opposite second surface 553, *a second substrate* 560 (520) supported by the first substrate 550 having a first surface 561, an opposite second surface 563, a body portion 502 between the first surface 561 and the second surface 563, a first side surface 565, and an opposite second side surface 567. As shown, *the body portion 502 defines a first passage 511 therein between the first side surface 565 and the second side surface 567*, and a first openings 569 on the first surface 561 of the second substrate 560 that are in fluid communication with the first passage 511. *Sidewalls 571, 573, 575 are positioned over the first surface 561 of the second substrate 560. A third substrate 580 is positioned over the sidewalls 571, 573, 575 and the second substrate 560*, with a first surface 581 and an opposite second surface 583. The sidewalls 571, 573, 575, partition the space between the second substrate 560 and the third substrate 580 into chambers 590, 592, above the first surface 561 of the second substrate such that only one of the first openings 569 distributed on and over the first surface 561 of the second substrate is located between the sidewalls of a corresponding chamber 590, 592. *Each chamber 590, 592 is in fluid communication with at least one neighboring chamber through a second passage 593 defined over a corresponding sidewall 571, 573, 575 and under the second surface of the third substrate 583.* Sensors 505 are positioned in the first passage 511 proximate to a corresponding one of the first openings 569. Each cell 501 is positioned in a corresponding chamber 590, 592 and the intracellular space 543 of each cell 501 is in fluid communication with the first passage 511 through the first openings 569. Seal elements 503 are positioned on the second substrate 560 and proximate to a corresponding first opening 569, for sealing each cell 501 to the second substrate 560 in operation. *First controls 509A, 509B, 509C are positioned inside the first passage 511, for*

*controlling the flow of a medium through the first passage 511. Second controls 521A, 521B, and 521C are positioned inside the second passage 593, for controlling the flow of a medium through the second passage 593.*

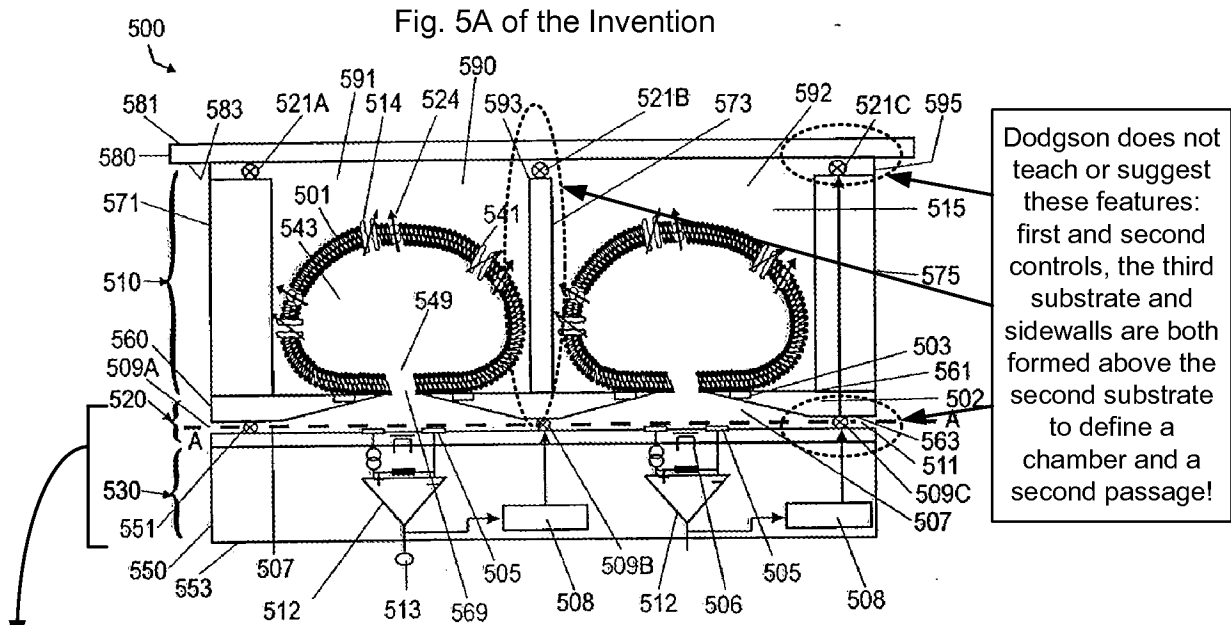
As the Examiner conceded in the March 28, 2008 Office Action, Dodgson does not disclose, teach or suggest a device in which “*a third substrate and sidewalls are both formed above the second substrate to define a reaction chamber and a second passage*”, as claimed in claim 1 of the present invention. Furthermore, Dodgson does not disclose, teach or suggest a device having “*a first pair of fluid controls positioned in the first passage, and a second control positioned inside the second passage,*” as claimed in claim 1 of the present invention.

Additionally, Applicant respectfully submits that Dodgson does not disclose, teach or suggest a device that includes *a second substrate* having a first surface and a second surface defining a body portion therebetween, where *the body portion defines a first passage therein between the first and second side surfaces*, as recited in amended claim 1 of the present invention.

In contrast, as shown in Fig. 1 of Dodgson, Dodgson discloses an apparatus for making measurements on small objects such as cells or liposomes, which has “a test position 10 ... in which a substrate 12 has a channel 14 within it, opening to an orifice 16 at a location at which an object such as a cell is to be tested.” (Dodgson, [0001] and [0036].) The object such as a cell 30 in a test position 10 covers the orifice 16. As shown in Fig. 3 of Dodgson, which is provided below, the Dodgsonian apparatus has at least *four separate substrates: a first substrate, a second substrate* positioned over the first substrate and separated from it by a “suction channel” 52, *a third substrate* positioned over the second substrate and separated from it by an “additional channel” 50, and *a fourth substrate* positioned over the third substrate and separated from it by a channel 18 (see also Fig. 1 of Dodgson). A channel 14 defined by the second substrate connects between the suction channel 52 and the additional channel 50. The channel 18 and the additional channel 50 are in fluid communication through an opening defined by the third substrate. A first electrode 24 is placed in the suction channel 52 on the first substrate and a second electrode 26 is placed in the channel 18 on the third substrate, respectively. The additional channel 50 and the channel 18 are characterized by the Examiner as a first passage and a second passage, respectively. In other words, in Dodgson, the additional channel 50 (*the first passage*) is *defined*

*by and between the second substrate and the third substrate, and the channel 18 (the second passage) is defined by and between the third substrate and the fourth substrate.*

Therefore, Dodgson *teaches away* from a device having “a first substrate ...; *a second substrate* supported by the first substrate, the second substrate having a first surface, an opposite second surface, a body portion between the first surface and the second surface, a first side surface and an opposite second side surface, wherein *the body portion defines a first passage therein between the first side surface and the second side surface*, and *a first opening* on the first surface of the second substrate that is in fluid communication with the first passage; *sidewalls positioned above the first surface of the second substrate; a third substrate positioned over the sidewalls and the second substrate* and having a first surface and an opposite second surface, *wherein the third substrate, the sidewalls and the second substrate define a chamber*, and wherein the chamber is in fluid communication with *a second passage defined by portions of the sidewalls and the third substrate*; ... *a pair of first controls* positioned inside the first passage, between the first surface of the first substrate and the second surface of the second substrate, for controlling the flow of a medium through the first passage; and *a second control* positioned inside the second passage, for controlling the flow of a medium through the second passage”, as recited in amended claim 1 of the present invention.



The second substrate 560/520 defines a first passage 511 therein, and is supported by the first substrate 550/530. No gap (channel) is formed between the first and second substrate.

They are distinctly different!

The first passage 50 is defined by and between the second substrate and the third substrate, and a channel 52 is defined by and between the first substrate and the second substrate.

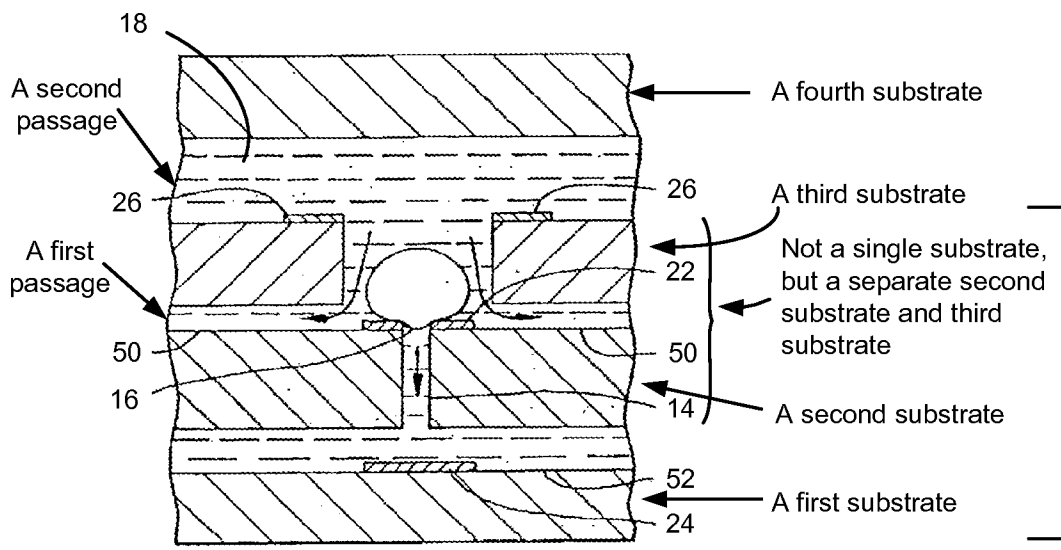


Fig. 3 of Dodgson

Additionally, Klemic discloses “*planar polymer electrodes for making patch clamp measurements of ionic currents through biological membranes*, such as the plasma membranes of living cells.” (Klemic, Abstract) As shown in Figs. 1-3 and 10 of Klemic, which Fig. 3 is provided below, the electrodes comprises “*a silicone polymer* molded so as to form *a partition* comprising *an aperture* ...; and *a backplate* associated with the apertured-partition, said backplate comprising an electrically conductive contact, wherein the association of the apertured-partition and the backplate forms *a compartment* associated with the aperture, ...” The electrodes also include “*walls* associated with the electrodes so as to form *chambers*”, (Klemic, col. 3, lines 66 and 67 through col. 4, lines 1-11. Emphasis added.) The electrodes further include “*one or more microfluidic channels associated with the backplate*”, which is “*incorporated into a poly-dimethylsiloxane [PDMS] layer of the backplate*”. Preferably, the one or more microfluidic channels is “*fabricated into the backplate*”. The electrodes also include “*one or more microfluidic valves* associated with the backplate”, which are “*incorporated into a poly-dimethylsiloxane [PDMS] layer of the backplate*”. Preferably, the one or more microfluidic valves are “*fabricated into the backplate*”. (Klemic, col. 4, lines 65-67 through col. 5, lines 1-15. Emphasis added.)

In the Office Action, the Examiner asserted that “Klemic teaches that *a first substrate in the form of a backplate* is provided. *A second substrate in the form of a dual PDMS layer* is supported by the backplate,” and “*the second substrate includes a plurality of microfluidic channels*, thus forming at least one first passage in the second substrate.” However, as disclosed in Klemic and described above, *the one or more microfluidic channels are fabricated into the backplate* and *the one or more microfluidic valves are fabricated into the backplate*. Therefore, it is respectfully submitted that Klemic does not disclose, teach or suggest a device that includes “a first substrate ...; *a second substrate* supported by the first substrate, the second substrate having a first surface, an opposite second surface, a body portion between the first surface and the second surface, a first side surface and an opposite second side surface, wherein *the body portion defines a first passage therein between the first side surface and the second side surface*, and *a first opening* on the first surface of the second substrate that is in fluid communication with the first passage; *sidewalls positioned above the first surface of the second substrate; a third substrate positioned over the sidewalls and the second substrate* and having a

first surface and an opposite second surface, *wherein the third substrate, the sidewalls and the second substrate define a chamber*, and wherein the chamber is in fluid communication with *a second passage defined by portions of the sidewalls and the third substrate; ... a pair of first controls* positioned inside the first passage, between the first surface of the first substrate and the second surface of the second substrate, for controlling the flow of a medium through the first passage; and *a second control* positioned inside the second passage, for controlling the flow of a medium through the second passage” recited in amended claim 1 of the present invention.

Therefore, neither Dodgson nor Klemic, taken alone or in combination, discloses, teaches or suggests a device that includes “a first substrate ...; *a second substrate* supported by the first substrate, the second substrate having a first surface, an opposite second surface, a body portion between the first surface and the second surface, a first side surface and an opposite second side surface, wherein *the body portion defines a first passage therein between the first side surface and the second side surface*, and *a first opening* on the first surface of the second substrate that is in fluid communication with the first passage; *sidewalls positioned above the first surface of the second substrate; a third substrate positioned over the sidewalls and the second substrate* and having a first surface and an opposite second surface, ... *a pair of first controls* positioned inside the first passage for controlling the flow of a medium through the first passage; and *a second control* positioned inside the second passage for controlling the flow of a medium through the second passage,” as recited in amended claim 1 of the present invention.

Accordingly, applicant respectfully submits that the Examiner has failed to make a *prima facie* case to support the rejection to claim 1 under 35 U.S.C. §103(a) over Dodgson in view of Klemic. In supporting the obviousness rejections under 35 U.S.C. §103, the Examiner “bears *the initial burden...of presenting a prima facie case of unpatentability*...After evidence or argument is submitted by the applicant in response, patentability is determined *on the totality of the record*.” *Ex parte Wada and Murphy*, BPAI Appeal No. 2007-3733 (January 14, 2008), and “*Office personnel must articulate*”, among other things, “*a finding that the prior art included each element claimed ...*”, MPEP 2143 (A)(1). The “*unwitting application of hindsight*” is *inappropriate*. *Ex parte So and Thomas*, BPAI Appeal No. 2007-3967 (January 4, 2008). In other words, the Examiner’s “rejections on obviousness cannot be sustained with mere conclusory statements; instead, there must be some articulated reasoning with some rational



underpinning to support the legal conclusion of obviousness.” *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006). (MPEP §2142). (Emphasis added.)

Fig. 5A of the Invention

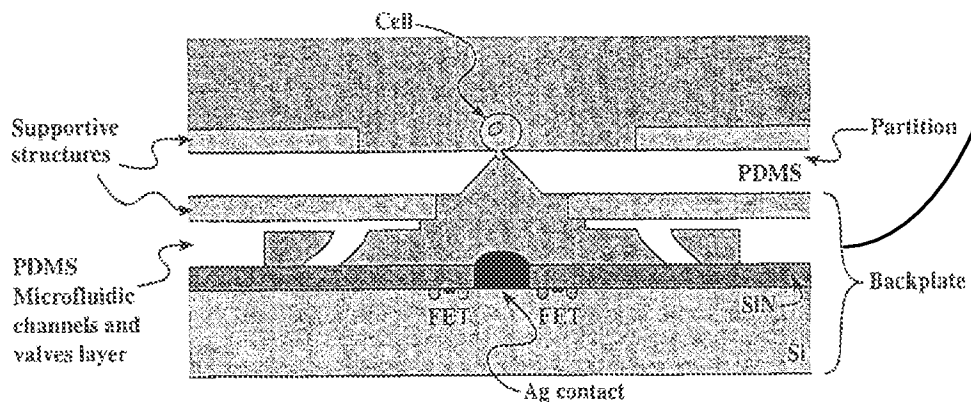
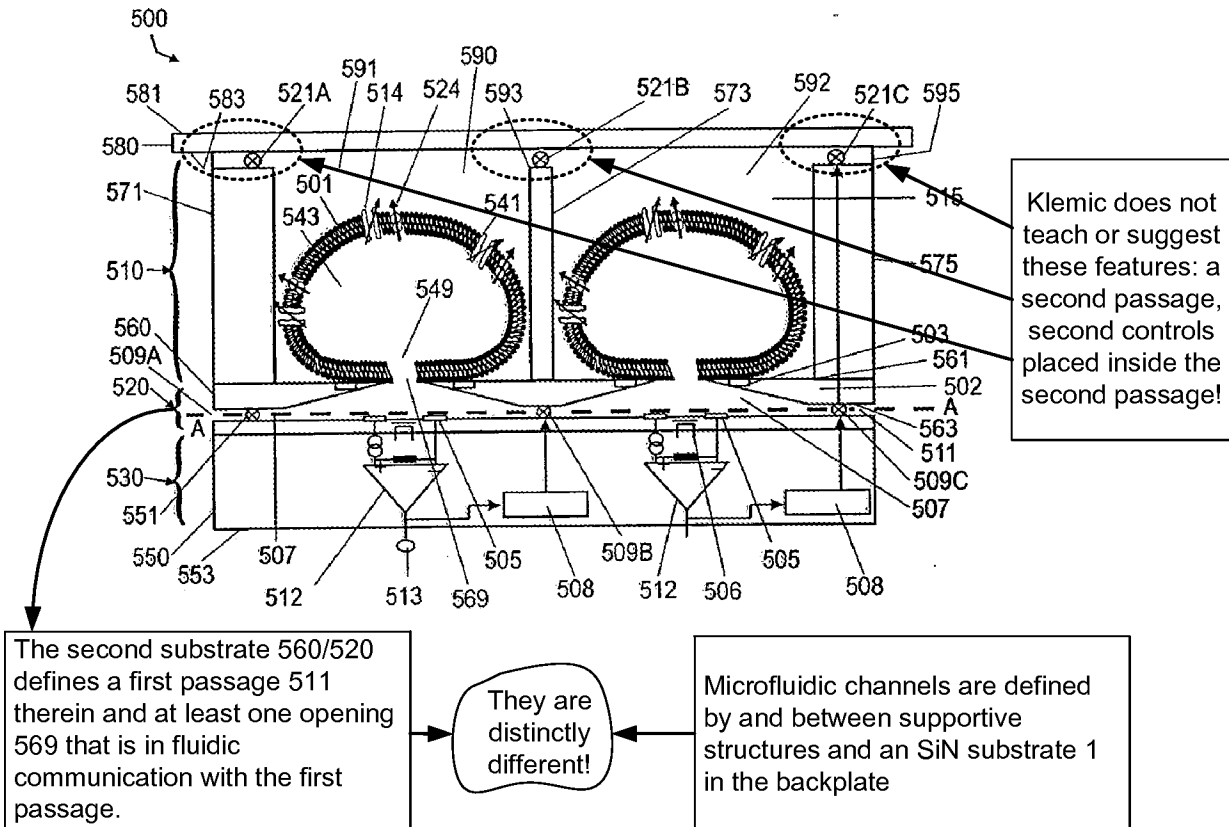


Fig. 3 of Klemic

For at least the foregoing reasons, independent claim 1, as amended, is patentable under 35 U.S.C. §103(a) over Dodgson and Klemic.

Accordingly, claims 2-7, 10, 11 and 75-77, which depend from allowable claim 1, are patentable for at least this reason.

Furthermore, claims 2-7, 10, 11 and 75-77 also contain additional patentable subject matter. For example, claim 2 recites a limitation of “wherein the membrane of the cell defines a second opening through which the intracellular space of the cell is in fluid communication with the first passage through the first opening.” Neither Dodgson nor Klemic, taken alone or in combination, discloses, teaches or suggests a device having the limitation. Accordingly, Applicant respectfully requests that each of these claims be examined individually.

**Claim 12-20, 23, 24 and 78-81:**

As set forth above, amended claim 12 recites a device for monitoring status of a plurality of cells, wherein each cell has a membrane forming a substantially enclosed structure and defining an intracellular space therein, that requires:

- “a. a first substrate having a first surface and an opposite second surface;
- b. ***a second substrate*** supported by the first substrate, the second substrate having a first surface, an opposite second surface, a body portion between the first surface and the second surface, a first side surface and an opposite second side surface, wherein the body portion ***defines a first passage therein between the first side surface and the second side surface*** and a plurality of first openings distributed on and over the first surface of the second substrate, wherein each of the plurality of first openings is in fluid communication with the first passage;
- c. a third substrate positioned over the second substrate, having a first surface and an opposite second surface, and spaced apart from the second substrate thereby defining a space between the second surface of the third substrate and the first surface of the second substrate;
- d. a plurality of sidewalls positioned between the second substrate and the third substrate thereby partitioning the space between the second substrate and the third substrate into a plurality of chambers above the first surface of the second

substrate such that only one of the first openings distributed on and over the first surface of the second substrate is located between the sidewalls of a corresponding chamber, *wherein each chamber is in fluid communication with at least one neighboring chamber through a second passage defined over the sidewalls and under the second surface of the third substrate;*

- e. a plurality of sensors positioned in the first passage, each sensor being proximate to a corresponding one of the first openings distributed on and over the first surface of the second substrate, wherein each cell is positioned in a corresponding one of the chambers and the intracellular space of each cell is in fluid communication with the first passage through the first opening located between the sidewalls of a corresponding chamber;
- f. a plurality of seal elements positioned on the second substrate for sealing a corresponding cell to the second substrate in operation, wherein each seal element is proximate to a corresponding one of the plurality of first openings;
- g. *a plurality of first controls positioned inside the first passage, wherein each chamber has a pair of corresponding first controls for controlling flow of the medium through portions of the first passage that correspond to that chamber; and*
- h. *a plurality of second controls, wherein each second control is positioned inside a corresponding second passage for controlling the flow of a medium through that second passage.*” (Emphasis added.)

Referring to and incorporating herewith the reasons set forth above why amended claim 1 is patentable under 35 U.S.C. §103 over Dodgson and Klemic, Applicant respectfully submits that independent claim 12, as amended, is patentable under 35 U.S.C. §103(a) over Dodgson and Klemic for at least these reasons.

Accordingly, claims 13-20, 23, 24 and 78-81, which depend from allowable claim 12, are patentable for at least this reason.

Moreover, claims 13-20, 23, 24 and 78-81 also contain additional patentable subject matter. For example, claim 13 recites a limitation of “wherein the membrane of each cell defines a second opening, through which the intracellular space of the cell is in fluid communication

with the first passage through the first opening located between the sidewalls of a corresponding chamber.” Applicant respectfully submits that neither Dodgson nor Klemic, taken alone or in combination, discloses a device having the limitation. Accordingly, Applicant respectfully requests that each of these claims be examined individually.

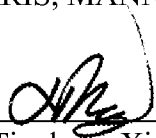
**CONCLUSION**

Applicant respectfully submits that the foregoing Preliminary Amendment and Response place this application in condition for allowance. If the Examiner believes that there are any issues that can be resolved by a telephone conference, or that there are any informalities that can be corrected by an Examiner’s amendment, please call the undersigned at 404.495.3678.

Respectfully submitted,

MORRIS, MANNING & MARTIN, LLP

April 24, 2008

  
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